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FDA Compliance for Drug Recalls & Withdrawals

by Barton Cobert, M.D.

BLCMD Associates LLC

Date: Thursday, October 21, 2010

Time:

1:00pm – 2:30pm	**Eastern Daylight Time** (GMT/UT 1700)
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FDA Compliance for Drug Recalls & Withdrawals

An FOI Services, Inc. Teleconference

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BLCMD Associates LLC

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This presentation cites many websites for additional information. If you are using a paper copy of these notes, you can avoid typing URLs by using the live links on the slides online at www.foiservices.com/with6356

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Agenda

- Introduction
- Definitions: Recalls & Withdrawals
  - Regulatory Matters – U.S. & Abroad
- Root Cause Analysis
- Procedural Documents for Recalls & Withdrawals
- How to Create the Company Team to Handle the Issue
- Outsourcing Certain Functions
- Avoiding a Crisis & Managing a Crisis
- After the Withdrawal - Next Steps
- Government Inspections & Internal Audits/Quality System

Introduction

- Recalls are common
- An example: FDA Enforcement Report for the week of October 6, 2010

  http://www.fda.gov/Safety/Recalls/EnforcementReports/ucm228605.htm

  – Classes I & II: 38 food recalls covering hundreds of products including food supplements with steroids, chocolate, orange juice, roast beef, bread, kale, sunflower seeds

  – Classes I & II: 97 drug/biologic and 22 device products covering thousands of products including Lipitor®, lidocaine gel, midazolam injection, blood products, monoclonal antibody reagents, neuroballoon catheters, diagnostics

  – Includes domestic and imported products from such entities as Pfizer, American Red Cross and other big and small firms and non-profits.

U.S. Department of Health & Human Services www.hhs.gov

U.S. Food and Drug Administration A-Z Index Search go

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Safety

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Home > Safety > Recalls, Market Withdrawals, & Safety Alerts > Enforcement Reports

Recalls, Market Withdrawals, & Safety Alerts

Enforcement Reports

- 2009
- 2008
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Enforcement Report for October 6, 2010

October 6, 2010 **10-39**

RECALLS AND FIELD CORRECTIONS: FOODS - CLASS I

PRODUCT
Raw Shelled Pistachios, 80% whole, in 25 lb. plastic lined cardboard box. Recall # F-2896-2010
CODE
Produced on 04/30/2010, 05/18/2010, 06/04/2010, 06/17/2010, 06/25/2010, and 07/06/2010
RECALLING FIRM/MANUFACTURER
California Delights, Inc., Newman, CA, by telephone on July 26, 2010. Firm initiated recall is ongoing.
REASON
Raw Shelled Pistachios may be contaminated with Salmonella.
VOLUME OF PRODUCT IN COMMERCE
96,000 lbs
DISTRIBUTION
MN, NV, AK, and Canada

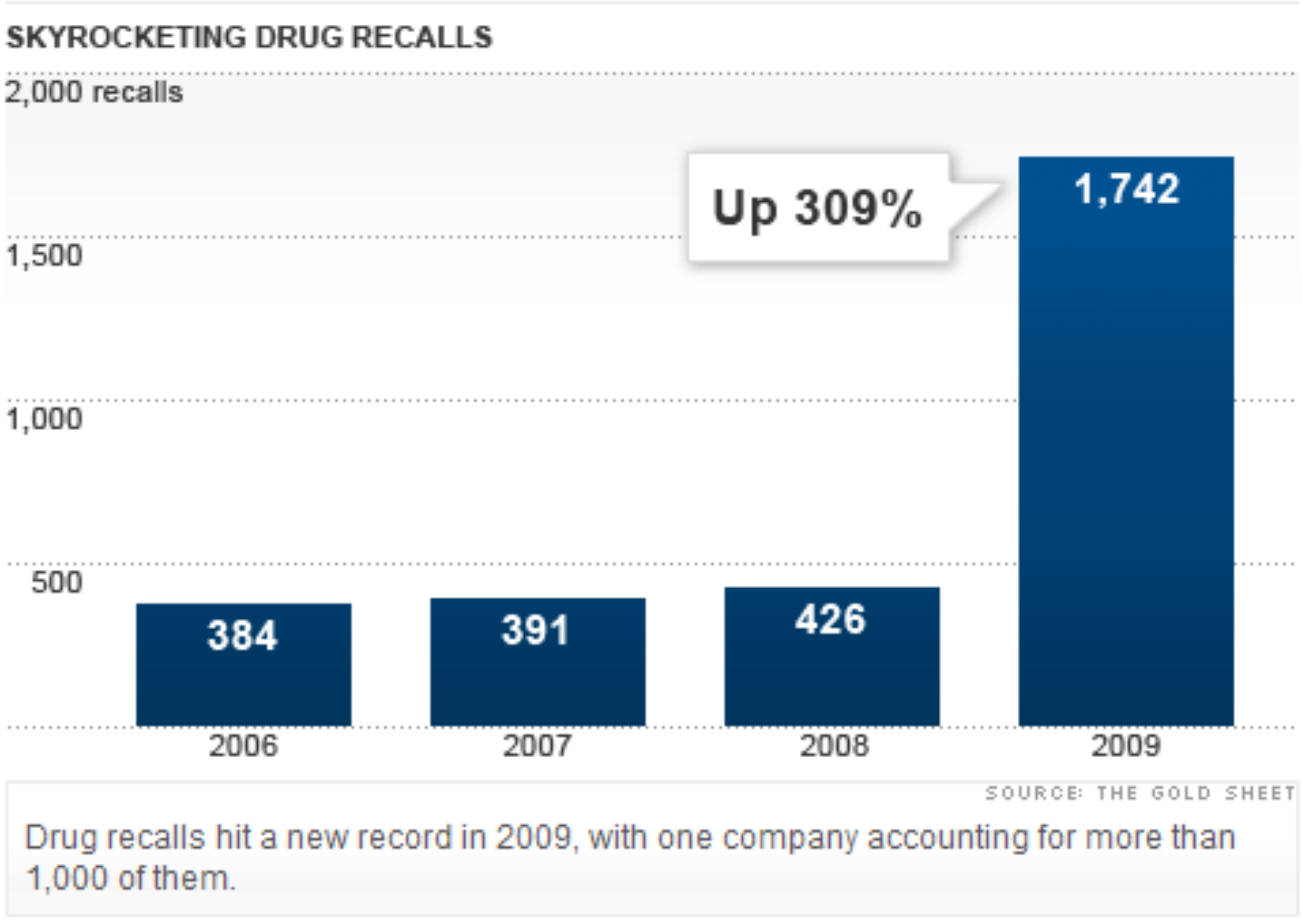
PRODUCT
Lipitor (atorvastatin calcium), tablets, 40 mg, 90 count bottle, Rx Only, NDC 0071-0157-23.
Recall # D-939-2010
CODE
Lots 0855020, 0819020, 0842020, 0843020, 0854020; All Exp 01/13
RECALLING FIRM/MANUFACTURER
Recalling Firm: Pfizer Inc., New York, NY, by letters on August 18, 2010.
Manufacturers: Pfizer Ireland Pharmaceuticals, Ringaskiddy, Co. Cork, Ireland;
Pfizer Manufacturing Deutschland Gmbh, Freiburg, Germany; Rexam, Las Piedras Puerto Rico. Firm initiated recall is ongoing.
REASON
Chemical Contamination: complaints of an uncharacteristic odor identified as 2, 4, 6 tribromoanisole.
VOLUME OF PRODUCT IN COMMERCE
4,607,808 bottles
DISTRIBUTION
Nationwide

RECALLS AND FIELD CORRECTIONS: BIOLOGICS - CLASS II

Recall vs. Withdrawal

- Recall:
  - A firm's removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority
- Withdrawal
  - A firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by the FDA, or which involves no violation.
  - http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Recalls/default.htm

Drug recalls surge



Drug recalls hit a new record in 2009, with one company accounting for more than 1,000 of them.

Regulatory Definitions
21 CFR 7.40

- Recall is an effective method of removing or correcting consumer products that are in violation of laws.
- Recall is a voluntary action… to protect the public health and well-being from products that present a risk of injury or gross deception or are otherwise defective.
- Recall is an alternative to an FDA-initiated court action.
- Recall may be undertaken voluntarily and at any time by manufacturers and distributors, or at the request of the FDA.
- Recall is generally more appropriate and affords better protection for consumers than seizure…or other court action [which] is indicated when a firm refuses to undertake a recall requested by the FDA.
- [Seizure will be done]…where the agency has reason to believe that a recall would not be effective, determines that a recall is ineffective, or discovers that a violation is continuing.

Evaluation & Classification
21 CFR 7.41

- An evaluation of the health hazard…will be conducted by an ad hoc committee of FDA to evaluate:
  - Whether any disease or injuries have already occurred from the use of the product.
  - Whether any existing conditions could contribute to a clinical situation that could expose humans or animals to a health hazard
  - Assessment of hazard to various segments of the population, e.g., children, surgical patients…with particular attention paid to the hazard to those individuals who may be at greatest risk.
  - Assessment of the degree of seriousness of the health hazard
  - Assessment of the likelihood of occurrence of the hazard
  - Assessment of the consequences (immediate or long-range) of occurrence of the hazard
  - On the basis of this determination, the FDA will assign a classification, i.e., Class I, Class II, or Class III

Recall Classification

- **Class I recall:** A situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.

- **Class II recall:** A situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

- **Class III recall:** A situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

- **Market withdrawal:** Occurs when a product has a minor violation that would not be subject to FDA legal action. The firm removes the product from the market or corrects the violation. For example, a product removed from the market due to tampering, without evidence of manufacturing or distribution problems, would be a market withdrawal.

- **Medical device safety alert:** Issued in situations where a medical device may present an unreasonable risk of substantial harm. In some cases, these situations also are considered recalls.

http://www.fda.gov/Safety/Recalls/ucm165546.htm

Recall Strategy
21 CFR 7.42

- A recall strategy will be developed by the FDA for an FDA-requested recall and by the recalling firm for a firm-initiated recall to consider:
  - Results of health hazard evaluation.
  - Ease in identifying the product.
  - Degree to which the product's deficiency is obvious to the consumer or user.
  - Degree to which the product remains unused in the market-place.
  - Continued availability of essential products.

- The FDA will review the adequacy of the firm's strategy & recommend changes as appropriate. Do not delay initiation of a recall pending review.

- Elements of a recall strategy:
  - *Depth of recall.* Depending on the hazard and extent of distribution, specify the level in the distribution chain to which the recall is to extend, as follows:
    - Consumer or user level, which may vary with product, including any intermediate wholesale or retail level; or
    - Retail level, including any intermediate wholesale level; or
    - Wholesale level.
  - *Public warning.* Reserved for urgent situations where other means for preventing use of the recalled product appear inadequate. The FDA will ordinarily issue such publicity. If the firm decides to issue its own warning it should be reviewed & approved by FDA. The public warning will be:
    - General public warning through the general news media, either national or local as appropriate, or
    - Public warning through specialized news media, e.g., professional or trade press, or to specific segments of the population such as physicians, hospitals, etc.
  - *Effectiveness checks should be done by the firm (with FDA assistance). Specify the method(s) to be used and the level:*
    - Level A--100 percent of the total number of consignees to be contacted;
    - Level B--Some percentage of the total number of consignees to be contacted, which percentage is to be determined on a case-by-case basis, but is greater that 10 percent and less than 100 percent of the total number of consignees;
    - Level C--10 percent of the total number of consignees to be contacted;
    - Level D--2 percent of the total number of consignees to be contacted; or
    - Level E--No effectiveness checks.

FDA Initiated Recall
21 CFR 7.45

- FDA may request a firm to initiate a recall when:
  - A product that has been distributed presents a risk of illness or injury or gross consumer deception.
  - The firm has not initiated a recall of the product.
  - An agency action is necessary to protect the public health and welfare.

- FDA will notify the firm of this determination and of the need to begin a recall immediately specifying the violation, the health hazard classification of the violative product, the recall strategy, and other instructions.
  - The firm may be asked to provide the FDA with information.

Firm-Initiated Recall
21CFR 7.46

- A firm may decide of its own volition and under any circumstances to remove or correct a distributed product if the firm believes the product to be violative. The firm is to notify immediately the FDA district office and provide:
  - Identity of the product involved.
  - Reason for the removal and the date and circumstances the issue was discovered.
  - Evaluation of the risk.
  - Total amount of such products produced and/or the timespan of the production.
  - Total amount of such products estimated to be in distribution channels.
  - Distribution information, including the number of direct accounts and, where necessary, the identity of the direct accounts.
  - A copy of the firm's recall communication if any has issued, or a proposed communication if none has issued.
  - Proposed strategy for conducting the recall.
  - Contact information of the firm official who should be contacted concerning the recall.
- FDA will review & advise the firm of the assigned recall classification, any changes in the firm's recall strategy and place the information in the weekly FDA Enforcement Report. The firm need not delay initiation of the recall.
- A firm may decide to recall a product when informed by FDA that it has determined that the product in question violates the law, but the agency has not specifically requested a recall.
- The firm should consult with FDA district office when the reason for the recall is not obvious or clearly understood but where it is apparent, e.g., because of complaints or adverse reactions regarding the product, that the product is deficient in some respect.

Recall Communication

21 CFR 7.49

- *Responsibility.*
  - The firm is responsible for promptly notifying each of its affected direct accounts to convey:
  - The product being recalled.
  - That further distribution or use of any remaining product should cease immediately.
  - Where appropriate, that the direct account should in turn notify its customers who received the product about the recall.
  - Instructions regarding what to do with the product.

- *Implementation.*
  - Use a first class letter … conspicuously marked, preferably in bold red type, on the letter and the envelope “drug/biologic recall marked "urgent“ for class I and class II recalls and, when appropriate, for class III recalls.
  - Telephone calls or other personal contacts should ordinarily be confirmed by letter.

- *Contents.*
  - Be brief and to the point;
  - Identify clearly the product, size, lot number(s), code(s) or serial number(s) and any other pertinent descriptive information to enable accurate and immediate identification of the product;
  - Explain concisely the reason for the recall and the hazard involved, if any;
  - Provide specific instructions on what should be done with respect to the recalled products; and
  - Provide a ready means for the recipient of the communication to report to the recalling firm whether it has any of the product, e.g., by sending a postage-paid, self-addressed postcard or by allowing the recipient to place a collect call to the recalling firm.
  - The recall communication should not contain irrelevant qualifications, promotional materials, etc.
  - Follow-up communications should be sent to those who fail to respond to the initial recall communication.

- *Responsibility of recipient.*
  - Firms that receive a recall communication should immediately carry out the instructions.

Public Notification of Recall

21CFR 7.50

The FDA will promptly make available to the public, in the weekly FDA Enforcement Report, each new recall according to its classification, FDA or firm-initiated and the actions taken.

Recall Status Reports

21CFR7.53

- The firm is to submit periodic recall status reports to the FDA district office so that the agency may assess the progress of the recall at a frequency determined by the FDA depending upon the urgency of the recall; generally the reporting interval will be between 2 and 4 weeks.
- The recall status report should contain:
  - Number of consignees notified of the recall, and date and method of notification.
  - Number of consignees responding to th recall communication and quantity of products on hand at the time it was received.
  - Number of consignees that did not respond.
  - Number of products returned or corrected by each consignee contacted and the quantity of products accounted for.
  - Number and results of effectiveness checks that were made.
  - Estimated time frames for completion of the recall.

Termination of a Recall

21CFR 7.55

- A recall will be terminated when the FDA determines that:
  - All reasonable efforts have been made to remove or correct the product
  - It is reasonable to assume that the product subject to the recall has been removed.
- Written termination notification will be issued by the FDA district office.
- A firm may submit a written request for termination to the FDA and by accompanying the request with the most current recall status report and a description of the disposition of the recalled product.

Industry Guidance

21 CFR 7.59

General advice to firms:

- Prepare and maintain a current written contingency plan for recalls.
- Use sufficient (product/lot) coding of regulated products to make possible positive lot identification and to facilitate effective recall of all violative lots.
- Maintain product distribution records to facilitate location of products that are being recalled.

Biologics

- “Upon a determination that a batch, lot, or other quantity of a product licensed under this section presents an imminent or substantial hazard to the public health, the Secretary (i.e., FDA) shall issue an order immediately ordering the recall of such batch, lot, or other quantity of such product.”
- That is, FDA may issue an immediate order recalling a batch.
- Ref: 42USC§262(d)(1)

FDA Submission Instructions - 1

- Guidance for Industry of November 3, 2003

  http://www.fda.gov/Safety/Recalls/IndustryGuidance/ucm129259.htm

- Submit to FDA
  - Product Information:
    - Product name, product number(s), description (tablet, capsule, etc.), indications, expected shelf life, type of packaging, labeling (including private labels, package, case label, PI, etc.), NDA/ANDA/NADA Number, NDC Number, OTC or not, strength, route of administration
    - For devices: 510(k)/IDE/PMA number
    - For biologics: License & Registration number

FDA Submission Instructions - 2

- Codes
  - Lot/Unit Numbers, expiration dates, serial numbers (medical devices), UPC codes
- Recalling Firm:
  - Firm name, type (i.e. manufacturer, importer, broker, repacker, own-label distributor) & contact information
- Manufacturer:
  - Contact information
- Identify Firm Responsible for the Violation/Problem:
  - Contact information
- Reason for the Recall:
  - How product is defective and/or violative, how this affects the performance and safety of the product.
  - If the recall is due to the presence of a foreign object, describe the foreign objects' size, composition, hardness, and sharpness.
  - If the recall is due to the presence of a contaminant (cleaning fluid, machine oil, paint vapors), explain level of contaminant in the product. Provide labeling, a list of ingredients and the Material Safety Data Sheet for the contaminant.
  - If the recall is due to failure of the product to meet product specifications, provide the specifications and report all test results.
  - If the recall is due to a label/ingredient issue, provide and identify the correct and incorrect label(s), description(s), and formulation(s).
  - Please explain how the problem occurred and the date(s) it occurred.
  - Explain how the problem was discovered and the date discovered.
  - Please explain if the problem/defect affects ALL units subject to recall, or just a portion of the units in the lots subject to recall.
  - Explain why this problem affects only those products/lots subject to recall.
  - Provide detailed information on complaints: date of complaint, description of any injury or illness, lot numbers, MedWatch-MDRs
  - If a State agency is involved in this recall, identify Agency and contact.
  - Details for any Field Alert submitted

FDA Field Alert

- The purpose of the NDA Field Alert Program is to quickly identify drug products that pose potential safety threats.
- All drug manufacturers with NDAs and ANDAs must submit a Field Alert Report to the FDA district office if they find any significant problem with an approved drug within 3 days of a problem being identified:
  - any incident that causes the drug product or its labeling to be mistaken for or applied to another article,
  - bacterial contamination,
  - a significant chemical, physical change,
  - deterioration in the distributed drug product, and
  - failure to meet specifications of one or more distributed batches of the drug product.

FDA Submission Instructions - 3

- Health Hazard Assessment:
  - An assessment of the health risk associated with the deficiency.
  - A recall decision does not depend solely on the health risk of the product. Defective products and misbranded products where no health hazard exists are still in violation of the law and should be recalled.
  - For recalls of products such as human tissue and biological products include:
    - donor screening form, test results, including viral marker test results
    - SOPs that show the acceptance criteria for donor screening and/or viral marker testing, that was not met for the products subject to recall.

- Volume of Recalled Product:
  - Total quantity produced
  - Dates produced & distributed
  - Quantity distributed
  - Quantity on hold.
  - Quarantine status and mechanism
  - Estimate amount remaining in marketplace
    - distributor level
    - retail level
    - pharmacy or veterinary level (drugs)
    - user level (i.e. Medical Devices)
  - Provide the status/disposition of marketed product, if known, (e.g., used, transfused, implanted, used in further manufacturing, or destroyed).

FDA Submission Instructions - 4

- Distribution Pattern:
  - Direct accounts (customers you sell directly to):
    - wholesalers/distributors, repackers, manufacturers , retail/pharmacy, hospitals, clinics, laboratories, consumers, federal purchasers, foreign purchasers
  - Geographic areas of distribution, including foreign countries.
  - Provide a list & contact information to the District Office & whether if they were sold, shipped, may have been sold, product.
  - If under government contract, provide details. Include school lunch programs.
  - Notify all ship to and bill to customers.

- Recall Strategy:
  - Indicate the level in the distribution chain of the recall. (i.e. wholesale/retail/pharmacy/medical user) If your recall only extends to the wholesale/distributor level, explain rationale for not recalling to retail/pharmacy level.
  - Indicate the method of notification (i.e. mail, phone, facsimile, e-mail) & how done (first class mail, overnight, certified etc.).
  - If initial notification is by phone, send the phone script to FDA.
  - If you have a web site, you should consider posting the recall notification. This is not recommended as a sole means of customer notification.
  - Report on what you have instructed customers to do with the recalled product.
  - If product is to be returned, explain the mechanics of the process.
  - Explain if this recall will create a market shortage that will impact on the consumer.
  - Report on recall effectiveness check strategy. Include your actions for non- responders, out-of-business distributors.
  - Provide a proposed method of destruction, if applicable.
  - Notify the District prior to product destruction. FDA may choose to witness the destruction.
  - Keep full documentation.
  - Misbranded drugs for re-labeling should be returned to the recalling firm & contact the District office prior to release of reconditioned goods

FDA Submission Instructions - 5

Public Notification

- Press Release
  - If the product may pose a significant health hazard and recalled product is in the hands of consumers, a prompt press release is usually appropriate. Consult with FDA first. A joint press release with FDA may be appropriate.
  - The FDA will issue a Press Release if the firm has failed to do so, or if the firm-initiated press release is not adequate.

Recall notifications & envelopes should be flagged in large bold print "**URGENT RECALL**" & include:

- Product Identification:
  - Description of the problem and any potential health hazards:
  - Depth of the recall:
    - If a subrecall to lower levels is required, include instructions & details

- Instructions to customers:
  - Recall instructions should be clear. For example: Remove product from sale; Cease distribution; Subrecall (if appropriate); Return product. Include a return response card or form. Send copies to the FDA district office.
  - All customers in the distribution chain should be notified of the recall.
  - FDA does not believe it is appropriate for a salesman to visit a doctor's office and remove product without notifying the physician and staff.
  - Physicians may be treating patients that may suffer or have suffered some adverse effect from the drug subject to recall. With knowledge of the recall and the reason for the recall, the physician can better evaluate a patient's condition and provide appropriate patient care.
  - FDA does not believe it is appropriate for a salesman or broker representatives to remove product from retail shelves without informing store management of the recall. Failure to inform store management of the recall could result in product that is in storage, in transit to the store, or returned by customers, being offered for sale. The salesmen or broker representatives may not have knowledge or access to the recalled products stored in back rooms. Recalled products that are in-transit to the store would then be sold to customers. Recalled products returned by customers may be placed back on store shelves.

FDA Submission Instructions - 6

- Evaluation of the Recall
  - Effectiveness of the Recall
    - Effectiveness checks for every recall should be done to verify your recall notification letter was received, read, understood and followed by the customer at all affected levels of the distribution chain.
    - If ineffective, take the necessary steps to make the recall effective.
      - FDA may contact a percentage of your customers to be sure the recall was done and was done effectively.
  - Recall Status Reports
    - Provide Recall Status Reports (usually monthly) to the District office including: Dates customers notified, number of customers notified and responding, quantity of product returned or accounted for, details of effectiveness checks.
  - Root Cause Analysis
    - Provide this information to the District office once the root cause has been established.
  - Corrective Actions to Prevent Recurrence
    - Put in place & notify District office of the CAPA.
  - Termination of the Recall
    - When all possible customer responses have been received and it is reasonable to assume that the recalled product has been recovered, corrected, reconditioned, or destroyed consider a termination. Provide such information to the District office for FDA to consider formal termination.

Recalls Outside the U.S.

- Requirements vary from country to country and reporting time-frames may be different.
- Reports usually need to be done in the local language.
- Agencies communicate with each other and publicize recalls on websites and in other media.
- Companies must have mechanisms available for (immediate) recalls in all markets they sell or distribute, license-out, etc.

Canadian Recalls

- Similar to U.S. requirements & rules
- Guidance on Product Recalls
  http://www.hc-sc.gc.ca/dhp-mps/compli-conform/recall-retrait/recall_proc-marche_retrait-eng.php
- A recall is done if the product
  - Is or may be hazardous to health, fails or may fail to conform with any claims relating to the effectiveness, benefits, performance characteristics or safety or does not comply with the Food and Drugs Act or Medical Devices Regulations.

E.U. Recalls

- “Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001on the Community code relating to medicinal products for human use”
- “Revised Procedure for Handling Rapid Alerts & Recalls Arising from Quality Defects”, EMEA, 18 July 2003 EMEA/INS/2567/03
- Quality Defects & Recalls EMA/INS/GMP/313510/2006 Rev 2
  - www.ema.europa.eu/Inspections/docs/CoCP/31351006enrev1.pdf
  - See also: http://www.picscheme.org/publication.php?download&file=cGktMDEwLTMtcmFwaWQtYWxlcnQtc29wLnBkZg

- Obligations of the competent authorities and of the MAH to do a recall:
  - If a medicinal product proves to be harmful under normal conditions of use.
  - If a medicinal product is lacking in therapeutic efficacy.
  - If the qualitative and quantitative composition of the product is not as declared.
  - The controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.
- Each member state then creates a mechanism to handle recalls.

U.K. Recalls

- A Guide to Defective Medicinal Products
  http://www.mhra.gov.uk/Howweregulate/Medicines/Importingandexportingmedicines/CON007572
- Covers responsibilities of all parties & is similar to the U.S. requirements.
- Recalls covered by The Defective Medicines Report Centre (DMRC) of the UK Medicines & Healthcare Products Regulatory Agency (MHRA)

MAH Obligations

- Supply to the DMRC:
  - Dates of manufacture and release of the affected product batch(es) to the market
  - An impact assessment quantifying the number of batches affected
  - Where admixture has occurred, dates of manufacture and release of the admixed product, closest to the complaint batch, batch sizes, pack size, date of first and last distribution to the market
  - Review of complaint records for reports of similar defects
  - Estimation of stock under the licence holder's control.
  - Has the same batch been distributed to other countries?
- If appropriate, quarantine any remaining stock in the company and wholesale supply chain while an investigation is carried out.
- The DMRC may also require:
  - A risk assessment
  - A review of all associated batch manufacturing, packaging, testing, release and distribution records for anomalies which may explain the suspected defect
  - Examination and retesting, if appropriate, of retained samples
  - Details of any actions to be taken by the licence holder to correct the defect in the future.
- The MAH & DMRC will then decide on a course of action

MAH & DMRC

1. Classification of the risk level:
   - Class 1: The defect presents a life threatening or serious risk to health
   - Class 2: The defect may cause mistreatment or harm to the patient, but it is not life-threatening or serious.
   - Class 3: The defect is unlikely to cause harm to the patient, and the recall is carried out for other reasons, such as non-compliance with the MA or specification.
   - Class 4: “Caution in Use” Notices where there is no threat to patients or no serious defect likely to impair product use or efficacy. These are generally used for minor defects in packaging or other printed materials.

2. Determination of Level of Recall: Distributor, Pharmacy, GP Office, Pharmacy, Patient
   - Class 1 usually goes to the patient level.
   - Most recalls are Class 2 or 3 and rarely go to the patient level.
   - In severe cases a Drug Alert to the health care profession and public may be required.

Wholesalers, distributers etc. should have in place detailed procedures of action to be taken when a recall occurs.

MAH Follow-Up

- The licence holder should draw their own conclusions regarding a suspected defect and present them to the DMRC for assessment.
- The investigation is only closed when the DMRC issues a formal closing letter after a final report is received from the licence holder.
- The licence holder should provide regular updates at least every 2 weeks with a summary reconciliation between the amount of product in the market and the amount returned.

The Practicalities

- Based on PDUFA (2007) and the issues of melamine-tainted animal food, contaminated heparin and human food issues, FDA has altered its recall procedures.

- Companies must now have a recall plan prepared and ready to put into action before the need for such a plan occurs.

- The plan should be a written document (SOP) which is reviewed and approved by the company's regulatory, quality, manufacturing and legal groups (at least).

Example SOP

- Upon recall situation identification, the head of regulatory affairs will be notified immediately (24/7).
- Within 24 hours (or sooner if urgent):
  - The recall team (regulatory, drug safety, manufacturing, QA, legal, sales, communications/medical information) will meet within 24 hours (or sooner if urgent) to implement the SOP
  - Manufacturing & Quality will identify all products, lots and distribution channels involved
  - Analysis by Medical/Drug Safety on health hazard
  - Root cause/Failure analysis
  - Decision on Class I, II, III & recall depth made by team & approved by management
  - Notification of FDA (field alert & HQ if necessary) and other HAs via subsidiaries/distributors
  - Implementation & tracking of status and effectiveness
  - Communication strategy to company, public, partners
  - Termination and closure of recall
  - Legal issues (lawsuits, insurance etc.)

Recall SOP

- Scope & Rationale
- Specification of steps to be taken in what order, by whom and timing (usually asap) when a recall situation is found or when a health authority requests one.
- Procedures:
  - Formation of team members & coordinator/chair
  - Evaluate information available
  - Obtain additional information
  - Identify the source of the problem
  - Determine the extent of the problem
    - Products, lots, distribution (countries, regions)
  - Determine current or possible health hazards and consequences
  - Decide to recall or not.
    - If yes, class & level of recall
  - Notification of & consultation with FDA & other health agencies, distributors, partners etc.
  - Create recall strategy and detailed plan
  - Implementation of recall
    - Internal resources
    - Out-sourced functions
  - Updating FDA & other health agencies
  - Effectiveness checks
    - Alterations in strategy if needed.

Practicalities: The Recall Decision

- Regulatory & legal determine if the law is being violated: adulterated, misbranded
  - Recall vs. withdrawal
    - Largely a legal decision
  - Notify FDA & other Health Authorities
    - If outside the U.S., company needs a global strategy; consider downsides of notifying one agency and not others even if not obligatory

Practicalities:
Health Hazard Assessment

Largely a medical decision

- Document population at risk, nature of the risk from the product, actions to increase or worsen the risk, likelihood of risk actually occurring
  - Is it possible/likely injury has already occurred?
  - Medical conditions that could mask the injury or risk
  - Vulnerable groups: children, elderly, pregnant
  - Severity of risk; short vs. long term; reversible vs. permanent; is treatment possible?
  - Dose/exposure to produce harm (e.g., only if overdose)
  - Medical intervention needed?
- Written evaluation by a physician, reviewed by management & legal. Submissable to health agencies.
- The hazard analysis usually should not comment on the recall status, class, depth etc. but just make a medical/health analysis.
- If Serious Adverse Events occur they must be submitted to the agencies by Drug Safety as appropriate (expedited/alert 15 day reports).

Practicalities: Recall Strategy

- Each strategy should be tailored to the situation & consider the health hazard, ease in identifying and removing the product, obviousness of product to the public, amount left in the market and whether it is an essential product.
- Thus some products must be removed immediately and others not at all.
- Discussions with the agencies are obligatory.
- Not all agencies will react in the same way making difficult situations if removal is required in one market and not others.
  - Consider the need for “all or none” removals globally.

Practicalities:
Recall Communication

- Also must be customized to the situation.
- Use of new communication methods, including internet and social media, though not addressed in the regs, must be considered. Should you “tweet” or post it on Facebook?
  - Negotiate with agencies.
  - No clear agency policies yet.

Practicalities:
Media Attention

- Some issues will make headlines & will be political, controversial & costly to you.
- The company should designate only one experienced spokesperson who is media savvy.
  - Everyone else should be instructed to refer questions to the spokesperson and/or Medical Communications.
- Coordinate global response both to other agencies & local media.
- Legal & Communications should be involved.

Practicalities: Consequences

- Expect a rapid or immediate GMP inspection from one or more health agencies if a significant issue is involved.
- If drug safety is involved, a pharmacovigilance inspection may also follow.
- Product liability attorneys may act (quickly) causing records, documents etc. to be requested in discovery.
  - Google the product name and “attorney” “lawsuit” “liability” to track interest by the plaintiffs’ bar.
- Insurance & political issues may also occur.
- Companies are not expected to be perfect by the agencies; recalls are expected to be handled judiciously to protect the public health and to examine the root cause to prevent recurrences.
- Perceptions matter. Be a good “corporate citizen”

Example 1:
A Steroid - Topical

- A topical steroid cream & ointment was manufactured by a pharma company using active ingredients purchased from a supplier of long-standing in the midwest.

- The supplier informed the company that a contaminant had been discovered in the manufacture of the product which should have been removed during the standard manufacture of the steroid such that minimal amounts would be found in the ingredient delivered to the company.

Example 1

- The manufacturer did a rapid due diligence review and found very small amounts the contaminant in the delivered active ingredient.

- The manufacturer calculated & determined that this contaminant would be “eliminated” (below the limits of detection) by the standard manufacturing process for the finished product.

- The hazard analysis by the physicians in drug safety revealed that even if the contaminant was present at detectable levels it would pose minimal to no danger to patients (including vulnerable patients).

Example 1

- The product was distributed globally.
- The company decided that a recall was not necessary.
- The FDA and most other health agencies agreed. However the Japanese HA felt that the product must be recalled from the Japanese market down to the consumer level. The company did so and informed the other health agencies. At this point several E.U. agencies then required recall which was done.
  No U.S. recall was done.

Example 1: Epilogue

- The pharma company found a new supplier and sued the supplier…and the supplier countersued.
- Records were subpoenaed for discovery and computer files were “frozen” and paper files locked.
- Company personnel had many months of preparation, testimony and reports to prepare with the corporate and outside attorneys.
- Ultimately, the cases were settled out of court.

Example 1: Lessons

- Even small recalls with no harm to the public can produce enormous cost and interruption of work.
- No recall required in the U.S. but it was required in Japan which triggered an E.U. recall. FDA still did not require a recall.
- Some litigation but minimal.

Example 2:
Topical OTC Fluoride Drops

- An OTC fluoride solution for children and babies dental health changed suppliers for the eye dropper used to administer the solution.

- It was discovered some months after marketing that the size of the drops were now significantly larger though this was not visible to the parent resulting in more fluoride per drop being administered.

Example 2

- The hazard analysis revealed that significant toxicity can occur, particularly in babies and children (GI distress at lower excess doses and severe toxicity including death at high doses).
- However, it would be necessary to ingest the entire bottle before toxicity occurred.
- Note that the total amount of fluoride per bottle was not changed, just the amount per drop.

Example 2

- The company did not feel a recall was necessary as the supply in the market was small and had already been out for 6 months with no AEs reported.
- The FDA disagreed noting that fluoride is also found in toothpaste and vitamins and that an overdose, particularly in babies, was possible.
- FDA also noted that this was an OTC product and it was possible that there would be no health care professional following the children.
- FDA requested a recall to the consumer level which the company did.

Example 2: Lessons

- With vulnerable patients, the threshold for recall is often lower, even if no AEs or other problems are seen.

- Careful supplier vigilance and supply chain tracking are necessary.

Example 3

- Due to a manufacturing problem several (exact amount unknown) canisters of a best selling inhaled corticosteroid for asthma apparently did not contain the active ingredient, but did contain the vehicle such that a spray did come out of the canister but no medication was present.

- This led to Class II recalls to the retail, wholesale and consumer level - [Product A] inhalers, 58,936,179 units; [Product B], 831,594 units; [Product C], 5,274,819 units; [Product D], 2,706,424 units in the U.S. and Canada.

Example 3

- There were both before, during and after the recall reports of lack of efficacy, AEs and deaths but no signals or increased frequency were found.

- The exact number of canisters without product was never fully identified.

Example 3

- An external audit revealed significant manufacturing problems and led to 2 Warning Letters from FDA regarding inhaler manufacture and 3 on other products dating back at least 2 years before the recall.
  - There was "an imbalance between quality and production, leaning considerably toward production"
  - "An in-process assay for the active ingredient in [the product] is not performed."

Example 3

- Major GMP issues were found and the company entered into a consent decree with the FDA to fix the quality problems.
- The company was fined $500,000,000.
- Major changes in process and management were made.
- The consent decree was finally ended 5 years later.

Example 4: McNeil April 2010

- McNeil Consumer Healthcare, in consultation with the U.S. Food and Drug Administration (FDA), is voluntarily recalling all lots that have not yet expired of certain over-the-counter (OTC) Children's and Infants' liquid products manufactured in the United States and distributed in the United States, Canada, Dominican Republic, Dubai (UAE), Fiji, Guam, Guatemala, Jamaica, Puerto Rico, Panama, Trinidad & Tobago, and Kuwait.

- McNeil Consumer Healthcare is initiating this voluntary recall because some of these products may not meet required quality standards. This recall is not being undertaken on the basis of adverse medical events. However, as a precautionary measure, parents and caregivers should not administer these products to their children. Some of the products included in the recall may contain a higher concentration of active ingredient than is specified; others may contain inactive ingredients that may not meet internal testing requirements; and others may contain tiny particles. While the potential for serious medical events is remote, the company advises consumers who have purchased these recalled products to discontinue use.

- The company is conducting a comprehensive quality assessment across its manufacturing operations and has identified corrective actions that will be implemented before new manufacturing is initiated at the plant where the recalled products were made.

Example 4: McNeil April 2010

- For recall information on certain Infant's Tylenol® & Children's Tylenol® Products: http://www.tylenol.com/page2.jhtml?id=tylenol/news/ndc_finder.inc
- For recall information on certain Infant's Motrin® & Children's Motrin® Products: http://www.motrin.com/page.jhtml?id=/motrin/include/prd_motrin_ndcfinder.inc
- For recall information on certain Children's Zyrtec® Products: http://zyrtec.com/econsumer/zyrtec/press.view?body=/zyrtec/pages/ndc_finder.jsp
- For recall information on all recalled products 2010: http://www.mcneilproductrecall.com/page.jhtml?id=/include/mpr_ndc_finder.inc
- To request a refund or product coupon: https://www.mcneilproductrecall.com/page.jhtml?id=/include/replacement_coupon.inc
- To see Frequently Asked Questions: http://www.mcneilproductrecall.com/page.jhtml?id=/include/faq.inc

Example 4: McNeil July 2010

- McNeil Consumer Healthcare, Division of McNEIL-PPC, Inc., is recalling 21 lots of over-the-counter medicines. The lots involved, listed below, are sold in the United States, Fiji, Guatemala, Dominican Republic, Puerto Rico, Trinidad & Tobago, and Jamaica.

- This action is a follow-up to a product recall that McNeil Consumer Healthcare originally announced on January 15, 2010, which was initiated following consumer complaints of a musty or moldy odor, which has been linked to the presence of trace amounts of a chemical called 2,4,6-tribromoanisole (TBA). The risk of serious adverse medical events is remote. This recall is being conducted with the knowledge of the U.S. Food and Drug Administration (FDA) .These lots are being added to the list of recalled products as a precautionary measure after a continuing internal review determined that some packaging materials used in the lots had been shipped and stored on the same type of wooden pallet that was tied to the presence of TBA in earlier recalled lots. All lots involved in the recall were produced before the January 15, 2010 recall, after which McNeil stopped accepting shipments of materials from its suppliers on that type of pallet.

- BENADRYL® Allergy ULTRATAB™ Tablets and MOTRIN® IB products, TYLENOL® Extra Strength Rapid Release Gels and BENADRYL® Allergy ULTRATAB™ Tablets

http://www.mcneilproductrecall.com/page.jhtml?id=/include/news_july.inc

J&J Discloses More State & Federal Recall Probes

- The feds aren't the only investigators interested in Johnson & Johnson's recent spate of recalls. The company disclosed that "multiple" state attorneys general have launched their own probes. Plus, the U.S. Attorney's Office in Philadelphia has apparently broadened its probe, issuing additional subpoenas for information about the recalls.

- The healthcare giant's consumer drug division has suffered a series of recalls, including a massive recall of children's drugs made at a plant in Fort Washington, PA, that has since been shut down for a production overhaul. Both that plant and another in Lancaster, PA, have drawn FDA enforcement actions after failing agency inspections. The company also drew fire during congressional hearings for a so-called "phantom recall" in which it hired contractors to buy up suspect packets of Motrin, rather than immediately declare an official recall.

- The Philadelphia U.S. Attorney's Office first issued one subpoena to the company for information related to the recalls; J&J disclosed in a regulatory filing Wednesday that the federal subpoenas requested "documents broadly relating to recent recalls," the *Wall Street Journal* reports. The state authorities have since made "civil investigative demands" as well.

- "[The company] and its subsidiaries are vigorously contesting the allegations asserted against them and otherwise pursuing defenses to maximize the prospect of success," J&J says in the quarterly filing. (*FiercePharma;* August 12, 2010)

Testimony: Mr. William C. Weldon, CEO, Johnson & Johnson, before the House Committee on Oversight and Government Reform on September 30, 2010

- I know that we let the public down. We did not maintain our high quality standards, and as a result, children do not have access to our important medicines.

- Although our medical experts and the FDA agreed that the health risk was remote, we believed the right course of action was to proceed with a broad precautionary recall and commence a complete reexamination of McNeil's manufacturing processes. We recognized then, and we recognize now, that we need to do better, and we will work hard to restore the public's trust and faith in Johnson & Johnson, and strive to ensure that something like this never happens again.

Testimony: Actions Taken

- First and foremost, we kept McNeil's Fort Washington facility shut down, and we are completely revamping the facility

- Johnson & Johnson is investing more than $100 million on facilities, equipment, and other improvements to our operations.

- McNeil began working with an independent, third-party consulting firm with expertise in manufacturing and quality systems…assisted McNeil in identifying issues with, and improving, McNeil's manufacturing methods, supply chain management, and overall quality practices…McNeil also made significant organizational changes in the quality and operations leadership… new vice president of quality assurance…new vice president of operations, appointed a new plant manager…new head of quality…

- …you raised questions about what you described as a "phantom recall" of two lots of 8-caplet Motrin vials that were distributed to certain retail establishments, primarily gas stations and convenience stores of Motrin products that took place in 2009…Based on what I have learned…it is clear to me that in retrospect, McNeil should have handled things differently.

Testimony: Actions Taken

- McNeil informed FDA officials about McNeil's plans for an in-store assessment and then a retrieval of any of the 8-caplet Motrin vials that remained available for sale. McNeil believed that this was an expeditious way to remove the remaining caplets from the convenience store shelves.

- I believe that McNeil acted with good intentions, and I do not view the use of a contractor to retrieve product, by itself, as inappropriate. The retrieval of product in this case was targeted and very comprehensive. But this episode was not a model for how I would like to see Johnson & Johnson companies approach problems with defective product when they arise, and I can assure the Committee that we are taking stock of the lessons learned.

http://graphics8.nytimes.com/packages/pdf/business/20100930_WeldonTestimony.PDF

Lessons Learned

- A recall may be a sign of deeper quality or manufacturing or safety problems.
- Continued vigilance is required at all levels and at all times.
- A quality system must be in place throughout the company.
- A solid SOP and system must be in place to handle recalls.

Lessons Learned

- For large scale recalls the company will need to mobilize resources in:
  - Manufacturing
  - Quality & Compliance
  - Regulatory
  - Sales
  - Drug Safety
  - Legal
  - Medical Communications
  - Others
- It is likely the company will not have the internal resources to be able to respond to all needs in an urgent manner and out-sourcing of some functions will be required.

Lessons Learned

- Do not try to hide anything or perform “phantom recalls.”
- Expect all involved health agencies around the world to take an active interest and to expect immediate action.
- Do not say one thing to one agency and a different thing to another agency.
- Senior management must be fully aware of and supportive of all efforts.
- The recall can become “all consuming” and interfere with normal daily work activities.

The Park Doctrine

- The Park doctrine allows the government to seek a misdemeanor conviction against company officials for alleged violations of the Federal Food, Drug, and Cosmetic Act (FDCA) - even if a corporate official was unaware of the violation - if the official was in a position of authority to prevent or correct the violation and did not do so.

The Park Doctrine

- *Park* Doctrine
  - Acme Supermarkets had problems with rat feces in the products they sold to the public. The CEO tried to remedy the problem after the federal government noted this but his efforts failed. Acme was sued & the company & CEO were found guilty.

  - The U.S. Supreme Court held that the law *"dispenses with the conventional requirement for criminal conduct - awareness of some wrongdoing".*

Park Doctrine

- The court explained, that for the greater good, the burden of compliance should rest upon those who, although otherwise innocent, stand responsible in relation to a public danger.

- The CEO, though not intending to harm, "*usually is in a position to prevent it with no more care than society might reasonably expect.*"

- Persons exercising authority or supervisory authority have not only a positive duty to remedy violations as they occur, but also a duty to implement policies and practices designed to insure against future violations.

Park Doctrine

- The accused CEO in this case claimed that he was *"powerless to correct or prevent the violation."* In defending against the charges (failure to store food properly & other cGMP issues), the CEO asserted that he had assigned this area of responsibility to subordinates.

- The court ruled that the CEO need not have participated directly in the situation but must only have had a *"responsible relationship"* to the violation.

Park Doctrine: The Bottom Line

In regard to FDA issues, if you have responsibility and bad things happen (e.g. ultimately harm to patients), you may be **civilly and criminally responsible** even though you are unaware of the specifics if you did not put in place reasonable written procedures to ensure compliance to the law.

Late-Breaking News

- A recent string of high-profile pharmaceutical and medical device product recalls appears to be reigniting FDA's interest in pressing misdemeanor charges against corporate executives under the Responsible Corporate Officer Doctrine, or Park Doctrine.
- Lewis Grossman, professor of law at The American University Washington College of Law, says that there now seems to be a growing attitude within the FDA that "working it out with the company and the company doing a voluntary recall is not enough." This will surely cause concern in the leadership of food and drug companies because, under some circumstances, the Park doctrine permits the misdemeanor conviction of a corporate officer who fails to prevent or correct a company regulatory violation – regardless of whether or not the officer knew of the violation.
- Indeed, the past few months have seen a number of FDA officials announce the agency's intention to be more aggressive in their punishment of companies for manufacturing violations. Speaking at the annual Food and Drug Law Institute Conference on April 22, Eric Blumberg, FDA's deputy chief counsel for litigation, revealed that "[v]ery soon, and I have no one particular in mind, some corporate executive is going to be the first in a long line…" The previous month, FDA Commissioner Margaret Hamburg wrote to Sen. Chuck Grassley, R-Iowa, informing him that the agency intends to "increase the appropriate use of misdemeanor prosecutions … to hold responsible corporate officials accountable."
- The Park Doctrine has rarely been employed since the 1980's but its seemingly imminent revival is sure to have corporate executives ill at ease. See here for our previous blog post and FDLI article on this topic.
- See: FDA Law blog August 29, 2010; by Oisin A. Mulvihill & Peter M. Jaensch http://www.fdalawblog.net/fda_law_blog_hyman_phelps/

Thank You!

If you have questions later, please don't hesitate to contact Bart via his website: www.blcmd.com

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by Barton Cobert, M.D., Presenter – October 21, 2010

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